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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,995	09/29/2000	Ravi V. J. Chari	104322.198 US1	2588

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EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	24

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.

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Commissioner for Patents

Advisory Action	Application No.	Applicant(s)	
	09/671,995	CHARI, RAVI V. J.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 May 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *15 May 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☒ Applicant's reply has overcome the following rejection(s): See attached Note of Explanation.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Note of Explanation*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *40,41, 44-89, 91, and 92*.

Claim(s) withdrawn from consideration: *1-32 and 90*.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *See Note of Explanation.*

Note of Explanation

1. The notice of appeal filed May 15, 2003 in Paper No. 22 is acknowledged and has been entered.

2. The amendment filed May 15, 2003 in Paper No. 23 is acknowledged and has been entered. Claims 14, 52, and 74 have been amended. Claims 90-92 have been added.

3. Claims 1-32, 40, 41, and 44-92 are pending in the application. Claims 1-32 and 90 have been withdrawn from further consideration pursuant to 37 CFR § 1.142(b), as being drawn to a non-elected invention. Claims 40, 41, 44-89, 91, and 92 currently stand rejected.

4. Applicants' grounds of traversal of the claim rejections set forth in the final Office action mailed November 19, 2002 (Paper No. 18) has been carefully considered and found persuasive in part. Accordingly, the following grounds of rejection set forth in the final Office action have been withdrawn:

(a) The rejection of claims 52 and 74 and claims 91 and 92 under 35 USC § 112, first paragraph for the reason set forth in section 6 of the final Office action.

Applicants have provided evidence that monoclonal antibody C242:II is known and publicly available.

US Patent No. 5,552,293-A discloses:

> C242:II is a monoclonal murine antibody of IgG class produced when culturing in an appropriate medium a hybridoma cell line obtained by fusing spleen cells from a mouse, which has been immunized with a human colonic adenocarcinoma cell line, with the murine myeloma cell line Sp2/0, as will be described in more detail in Example 1 below. A hybridoma cell line producing the C242:II antibody was deposited on Jan. 26, 1990 in accordance with the Budapest Treaty at the European Collection of Animal Cell Cultures (ECACC), PHLS Centre for Applied Microbiology and Research, Porton Down, Salisbury Wilts., U.K., where it obtained the depository accession number 90012601. Reference to his deposit has been made in our copending international patent application PCT/SE91/00496 (WO-A-9201470) that has priority from Jul. 20, 1990.

In addition, it is noted that the prosecution record of US Application 08/438,123, now issued as the above-mentioned US Patent No. 5,552,293-A, includes statement by an attorney of record having authority and control over the conditions of that stated deposit, over his or her signature

and registration number, that the deposit had been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits were to be irrevocably removed upon the grant of a patent on the application, and that the deposit would be replaced if viable samples cannot be dispensed by the depository. In addition, the prosecution record of US Application 08/438,123 includes a provision of assurances that all restrictions imposed by the depositor on the availability to the public of the deposited material were to be irrevocably removed upon the granting of the patent. See US Application 08/438,123; Paper No. 14, page 4.

Given the afore-mentioned disclosure, the assurances of record, and the claims (e.g., claim 2) encompassing antibody is produced by hybridoma cell line C242:II, which cell line has ECACC identification number 90012601 set forth in U.S. Patent No. 5,552,293-A, the conditions for the deposit of biological materials under 35 USC 112, first paragraph, with respect to monoclonal antibody C242:II have been satisfied; therefore, given the state of the art, the skilled artisan would be enabled to produce a humanized C242 antibody, such as is referred to in the present claims 91 and 92. However, it is duly noted that MPEP § 2404.01 states: "Those applicants that rely on evidence of accessibility other than a deposit take the risk that the patent may no longer be enforceable if the biological material necessary to satisfy the requirements of 35 U.S.C. 112 ceases to be accessible."

Applicants have provided evidence that monoclonal antibody N901 (NKH-1) is known and publicly available, as the antibody is currently commercially distributed by Beckman Coutler, Inc. See Paper No. 23, Exhibit L. MPEP § 2404.01 states:

> The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. See the final rule entitled "Deposit of Biological Materials for Patent Purposes," 54 FR 34864, 34875 (August 22, 1989). A product could be commercially available but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted.

The Examiner is unaware of any relationship between Applicants or Assignees and the commercial supplier of monoclonal antibody N901 (NKH-1). Therefore, absent knowledge of

such a relationship, the Office must accept the commercial availability as evidence that the monoclonal antibody N901 (NKH-1) is known and readily available to the public, so as to satisfy the statutory requirements for patentability under 35 USC § 112.

Although Applicants have attempted to rely upon the published disclosures of the antibodies, which are designated C242 or N901, the fact that the citations disclose the antibodies does not establish that upon issuance of a patent on this application, such material would be and continue to be accessible to the public. Applicants have not made of record the other investigators' policies, or any of the facts and circumstances that determine the public's accessibility to the biological materials from these other investigators, if a patent were to be granted upon this application. Furthermore, there is no assurance that these other investigators would allow unlimited access to the material, if a patent were to be granted upon this application.

(b) The rejection of claims 52 and 74 and claims 91 and 92 under 35 USC § 112, second paragraph for the reason set forth in section 8 of the final Office action.

Regarding claims 52 and 74, Applicants have identified an antibody designated N901 (NKH-1), which is known and currently commercially available to the public. Claims 52 and 74 are drawn to the composition or kit of claims 48 and 70, respectively, wherein said antibody is a "humanized N901" antibody; accordingly, the record presently reflects that Applicants regard the inventions as comprising a humanized version of commercially available N901 (NKH-1) or a fragment thereof.

Regarding claims 91 and 92, Applicants have identified an antibody produced by hybridoma cell line C242:II, which cell line has ECACC identification number 90012601 set forth in U.S. Patent No. 5,552,293-A, which is known and currently readily available to the public. Claims 91 and 92 are drawn to the composition or kit of claims 48 and 70, respectively, wherein said antibody is a "humanized C242" antibody; accordingly, the record presently reflects that Applicants regard the inventions as comprising a humanized version of an antibody, or fragment thereof, produced by hybridoma cell line C242:II, which cell line has ECACC identification number 90012601 set forth in U.S. Patent No. 5,552,293-A.

5. Applicants' arguments, otherwise, have been carefully considered but not found persuasive to overcome the remaining grounds of rejection set forth in the final Office action mailed November 19, 2002 (Paper No. 18) for the following reasons:

Regarding the rejection of claims 40, 41, 44-89, 91, and 92 under 35 USC § 103, Applicants have reiterated arguments set forth previously. The reasons that Applicants' arguments were not found persuasive have already been set forth in the final Office action mailed April 8, 2003 (Paper No. 14).

Nevertheless, as an additional reply to Applicants' assertion that Liu et al. teaches away from the claimed invention, because "Liu *et al.* teaches the effectiveness of monotherapy with no toxic side effects" (Paper No. 23, page 17, paragraph 3):

Although Liu et al. teach that an immunoconjugate comprising humanized C242 antibody conjugated to the maystansinoid DM1 is more effective than 5-fluoruracil (5-FU), Liu et al. does not address the effectiveness of treatments using a combination of the immunoconjugate and 5-FU, or any other chemotherapeutic agent. Therefore, Liu et al. does not teach away from the claimed invention, or suggest that a treating cancer using combination of agents would not be more effective than monotherapy.

Hotobagyi and Mendelsohn teach that combinations of anticancer therapeutic agents are more effective than monotherapies, as synergistic or additive effects are observed when combinations are used. Liu et al. teaches that the monotherapy comprising the immunoconjugate is highly effective, but the state of the art, at the time the invention was made, was such that it had been recognized that combinations, or cocktails of antitumor agents provide greater efficacy than monotherapy.

Liu et al. would not have dissuaded the artisan from combining the immunoconjugate and 5-FU, but it is duly noted that the claims are not so limited. *Arguendo*, however, if the disclosure of Liu et al. might have dissuaded the artisan, as Applicants have asserted, from combining the immunoconjugate and 5-FU to derive *an embodiment* of the claimed invention, Hortobagyi teaches a rationale for combining Docetaxel, in particular, with other therapeutic agents. In fact, Hortobagyi provides incentive to combine Docetaxel, rather than 5-FU, with other therapeutic agents under special circumstances, because Hortobagyi teaches that cancer cell lines that are resistant to 5-FU are not cross-resistant to Docetaxel. Therefore, to investigate the best possible

combination of agents to treat 5-FU-resistant cancer, Hortobagyi provide an impetus to combine Docetaxel, in particular, with other agents. Hortobagyi discloses numerous chemotherapeutic agents, including, for example, vincristine, cisplatin, etoposide, cyclonphosphamide, and methotrexate; and, at page 12, Hortobagyi teaches:

> Synergies, or at least additive effects, were observed in studies with two- and even three-drug combinations, including docetaxel, cyclophosphamide (Cytoxan, Neosar), fluorouracil (5-FU), vinorelbine, methotrexate, and etoposide (VePesid).

Furthermore, Mendelsohn teaches the combination of monoclonal antibody therapy and the chemotherapeutic agents, doxorubicin, cisplatin and paclitaxel, is currently under investigation, as prompted by the observations of synergistic antitumor activity of the combinations in pre-clinical trials.

It appears that Applicants have newly argued that it would only have been "obvious to try" to manufacture the claimed kit and composition, which the Examiner supposes amounts to an assertion that one of ordinary skill in the art would not have had a reasonable expectation of successfully producing such a kit and composition. The Examiner finds no reason to believe, however, that one of ordinary skill in the art would not have had more than a reasonable expectation of successfully producing such a kit and composition. Therefore, so long as one would have been motivated to produce the kit and composition, the Office's burden of establishing the *prima facie* obviousness of the inventions under 35 USC § 103(a) has been met. As stated in the Office action mailed May 24, 2002 (Paper No. 16) at pages 8 and 9:

> Mendelsohn teaches that combining a therapeutic chimeric antibody with a chemotherapeutic drug successfully eradicates well-established tumor xenografts that resist treatment with either agent alone (abstract).
>
> Hortobagyi teaches that synergies, or at least additive effects, were observed in studies with two- and even three-drug combinations. Hortobagyi concludes, "[t]he challenge is not only to find effective combinations, strategies, and regimens, but also to determine the optimal role for [docetaxel] in relation to many other active agents in development today" (page 14).
>
> One skilled in the art would have been motivated at the time the invention was made to manufacture such a kit, because the kit could be used to find effective combinations, strategies, and regimens, and to determine the optimal roles for one agents in relation to the others. For example, given the teachings of Liu, et al, one of ordinary skill in the art would have been motivated to determine if a combination of the immunoconjugate of Liu, et al and one or more of the chemotherapeutic agents be more effective than any of the agents alone, since both Mendelsohn and Hortobagyi teach that combination therapy is often more effective than monotherapy because synergistic or additive effects are often observed in the former. Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art to make a

> composition comprising one or the other immunoconjugates of Liu, et al and further comprising at least one of the chemotherapeutic agents currently under development and widely known in the art. One of ordinary skill in the art would have been motivated to use the kit to find the most effective combination of agents and to determine the optimal roles of one of the agents in relation to the others, because there had been a long-felt need for more efficacious antitumor therapies and for a greater understanding of the pharmacology of combination therapies.

Applicants have remarked that only improper hindsight analysis could have been used by the Examiner to conclude the obviousness of the claimed invention, citing *In re Geiger*, wherein the Court decided, "[a]t best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known [...] agents". In considering Applicants' argument, the question pondered by the Examiner is, to what purpose might Applicants believe it obvious only to try to produce the claimed invention? Admittedly, while it may only have only been obvious to try to *use* a particular combination of agents, e.g., a combination of the immunoconjugate disclosed by Liu et al. and paclitaxel, *to treat breast cancer*, for example, in view of the disclosures of Hortobagyi and Mendelsohn, it would have been obvious, if not commonsense to first combine different agents to identify a combination of agents that might best be used to treat breast cancer. Again, this is precisely the rationale upon which the obviousness under 35 USC § 103(a) of the claims has been concluded: one of ordinary skill in the art, given benefit of the disclosures of the prior art, would have been motivated to manufacture the claimed kit and compositions, as Hortobagyi suggests, "to find effective combinations, strategies, and regimens, but also to determine the optimal role for [docetaxel] in relation to many other active agents in development today" (Hortobagyi, page 14).

Furthermore, MPEP § 2145 states:

> "The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)

Using the analysis exemplified by the Court, the claimed method in this instance, would have been obvious over the prior art relied upon because the cited references contain a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.

In addition, Applicants have again argued, "it has been unexpectedly been discovered that claimed compositions of immunoconjugates and chemotherapeutic agents delay tumor growth longer than one would expect for an additive anti-tumor effect of the individual components" (Paper No. 23, page 19, paragraph 2). In reply, MPEP § 2141 states:

> The Supreme Court reaffirmed and relied upon the Graham three pronged test in its consideration and determination of obviousness in the fact situations presented in Sakraida v. Ag Pro, Inc., 425 U.S. 273, 189 USPQ 449, reh 'g denied, 426 U.S. 955 (1976) and Anderson 's Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 163 USPQ 673 (1969). In each case, the Court discussed whether the claimed combinations produced a "new or different function" and a "synergistic result," but it clearly decided whether the claimed inventions were nonobviousness on the basis of the three-way test in Graham. **Nowhere in its decisions in these cases does the Court state that the "new or different function" and "synergistic result" tests supersede a finding of nonobvious or obviousness under the Graham test** [emboldened for emphasis].

The Graham test has been applied appropriately and the conclusion of the obviousness of the claimed invention has been made accordingly.

Applicants have argued that the observation of unexpected, *synergistic* effects, as opposed to additive effects, renders the invention unobvious under 35 USC § 103(a). MPEP § 2141 further states:

> [S]ynergism may point toward nonobviousness, but its absence has no place in evaluating the evidence on obviousness. The more objective findings suggested in Graham, supra, are drawn from the language of the statute and are fully adequate guides for evaluating the evidence relating to compliance with 35 U.S.C. § 103. Bowser Inc. v. United States, 388 F. 2d 346, 156 USPQ 406 (Ct. Cl. 1967).

Applicants have remarked, "there is no mention that additive or synergistic effects are 'frequent' " (Paper No. 23, page 20, paragraph 2). In reply, Applicants are correct; rather, at page 12, Hortobagyi plainly states: "Synergies, or at least additive effects, were observed", period. Also, at the abstract, Mendelsohn plainly teaches: "mAb in combination with chemotherapy exhibits a synergistic antitumor activity", period. The additive or synergistic effect of combinations of antitumor agents was not unexpected at the time the invention was made. The fact that the mechanism of these additive or synergistic effects may not have been understood, is not reason to doubt the obviousness of the claimed invention.

Accordingly, Applicants' arguments have been carefully considered but not found persuasive.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
August 22, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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